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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,718	12/14/2001	Karl H. Weisgraber	UCAL-222	5282

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,718	WEISGRABER ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7 and 9-22* is/are pending in the application.

4a) Of the above claim(s) *9-13 and 16-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5, 7, 14, 15, 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application's Amendment and Response, filed 7/6/04, has been entered. Claims 1, 3, 5, 7 and 9-22 are pending. Claims 9-13 and 16-19 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8. Claims 1, 3, 5, 7, 14, 15, 20-22 are under current examination.

The Weisgraber Declarations (Exhibits 1 and 3), filed 7/6/04, have been considered.

New Matter

The amendment filed 7/6/04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment adds Figures 5A and 5B, which introduce new matter into the instant disclosure with regard to the human apoE4 sequence (SEQ ID NO: 1) and the alignment of sequences from various other species (SEQ ID NO: 2-13).

See also *Ex parte* Raible 8 USPQ2d 1709, which requires that "an incorporating statement clearly identify the subject matter which is incorporated and where it is to be found," *In re* de Seversky, MPEP §608.01(p).

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1, 3, 5, 7, 14, 15, 20-22 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is *withdrawn.*

Applicants' argue that the specification indicates that the mouse apoE, as well as nine other species contains a Thr residue at a position equivalent to the Arg-61 of the human apoE. Particularly, the specification provided a reference to Weisgraber *et al.*, and this reference includes the full amino acid sequences from apoE from various species, aligned with human apoE. Applicants argue that the Weisgraber reference was readily available to those skilled in the art as of the priority date of the application, and that the amino acid sequences in the reference were available to the public in 1991. Thus, Applicants argue that those skilled in the art would have appreciated that Applicants aligned the amino acid sequence of mouse apoE and human apoE, and identified the equivalent to Arg-61, using

standard alignment methods or computer program, and thus Applicants were in possession of the claimed invention. See p. 7, 1st ¶ of the Response.

Applicants' arguments are found to be persuasive with regard to the prior rejection because the claims, as written, are specifically directed to a modified apoE polypeptide comprising a Thr → Arg substitution at a position equivalent to the amino acid 61 of human apoE4. Thus, this modification describes a specific residue (a position equivalent to amino acid 61 of human apoE4) with a specific substitution (Thr → Arg) which results in a specific phenotype, that the resulting polypeptide exhibits preferential binding to lower density lipoproteins. Accordingly, the Examiner agrees that the claimed embodiment of a Thr → Arg substitution at a position to amino acid 61 of human apoE4, as claimed, fulfills the requirements of written description under 112, 1st paragraph.

Claims 1, 3, 5, 7, 14, 15, 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. The prior rejection is maintained.

Firstly, Applicants argue that the specification provides adequate guidance with regard to the human apoE4 amino acid sequence which be used to identify the amino acid equivalent in the mouse sequence. Applicants point to the specification,

which states that mouse apoE contains a Thr residue at a position equivalent to Arg-61 of the human apoE4, and that the Weisgraber reference, which was incorporated by reference includes the full amino acid sequences of apoE from various species aligned with human apoE4. Further, Applicants argue that this reference and the amino acid sequence of the mouse apoE were readily available to the public and those skilled in the art could have readily aligned the amino acid sequence of mouse apoE and human apoE4 and arrived at the alignment as shown in the Weisgraber reference. Further, Applicants point to the specification for teachings that the codon for the Thr-61 equivalent in the mouse apoE gene is located at the end of the third exon of the mouse apoE gene, exactly as it is in the human gene. See pp. 7-8 of the Response.

Applicants' arguments are found persuasive, because the human apoE4 and mouse apoE sequences were readily available to the public at the time the claimed invention was made, the specification provides sufficient guidance with regard to identification of the amino acid equivalent of the human Arg-61 in the mouse apoE sequence.

However, the prior rejection is maintained with regard to the argument that the instant specification fails to enable the methods of utilizing the claimed transgenic mouse in methods of identifying agents that reduce a phenomenon associated with Alzheimer's disease (AD) [see claim 14-15]. Firstly, Applicants point out that claims 1, 3, 5, 7, and 20-22 are not directed to methods of identifying an

agent that reduces a phenomenon associated with AD, but are directed to gene targeted mice and cells (see p. 9, 3rd ¶ of the Response). However, the prior rejection is maintained over the breadth of the claims because claims 14-15 are directed to methods of using the claimed mice. However, these claims are not found to be enabling because the specification has not provided a correlation between the phenotype of the claimed transgenic mice and AD. Applicants argue that the specification teaches that the animals of the instantly claimed invention would serve as models for human apoE4 domain interaction, and that these animals would be useful in drug screening assays, *e.g.*, to identify agents that reduce apoE4 domain interaction; and Applicants further point to the specification to show that phenomena associated with AD include amyloid deposits, neuronal cell loss and neurofibrillary tangles. See p. 10, 2nd full ¶. Thus, Applicants argue that the because the specification teaches how to determine whether a test agent reduces a phenomenon associated with AD, such as immunohistological assays for the presence of neuritic plaques, and that the a variety of methods of testing compounds for their effect on AD were known in the art as of the priority date of the instant application, the instant invention is enabling for the use of the claimed apoE4 transgenic mice in methods of identifying an agent that reduces a phenomenon associated with AD. See pp. 9-11 of the Response.

Applicants' arguments are not found to be persuasive. The transgenic mice of the instant invention exhibit a phenotype of preferential binding to lower density

lipoproteins when compared to a wild-type mouse. However, the specification fails to provide a correlation between the phenotype of the claimed transgenic mice and AD. Applicants argue that that they do not need to understand how an invention works to satisfy the enablement requirement, and that the art provides evidence that apoE, and particularly apoE4, is associated with AD. See p. 11 of the Response. This is not found to be persuasive. The specification must provide a nexus between the phenotype of the claimed mice [*i.e.*, that the modification of the endogenous mouse apoE4 causes the resulting polypeptide to exhibit preferential binding to LDLs] and a phenomenon associated with AD. For example, the specification fails to show that the claimed mice have more amyloid deposition or other phenotypes associated with AD. Accordingly, the instant specification fails to enable the instant invention because it fails to show how to use the claimed mice in methods of identifying agents that reduce a phenomenon associated with AD, because the phenotype of the claimed mice is not correlated with a phenomenon associated with AD.

Applicants provide Exhibit 1, the Weisgraber Declaration, which discusses a kainic acid injury model of neurodegeneration, wherein the Arg-61 gene-targeted mice of the claimed invention and wild-type mice were injected with kainic acid, and that it was found that the Arg-61 mice exhibited more neurodegeneration when compared to the wild-type control mice. Thus, Applicants conclude that the Arg-61 mouse, as claimed, is a model for neurodegeneration, a phenomenon associated with

AD. See p. 11, last ¶, of the Response. The Weisgraber Declaration has been considered, but not found to be persuasive. The Declaration shows that the transgenic Arg-61 mice are more susceptible to a particular compound, kainic acid, but in no way does the Declaration show that the Arg-61 mice are a model of AD. The mice themselves, absent the injection of kainic acid, do not exhibit any phenotypes which would make them models for AD. Thus, what the Declaration teaches provides no correlation that the mice would be models for AD, it merely shows that the mice have an increased susceptibility to kainic acid, which results in increased neurodegeneration. Furthermore, the Declaration states that kainic acid is a excitotoxin that over-stimulates neurons in the hippocampus, which results in the neurodegeneration of neurons. See p. 2, #4 of the Declaration. Thus, kainic acid causes neurodegeneration of neurons in wild-type and mutant mice. Although the mutant mice appear to have more neurodegeneration when exposed to kainic acid, this does not provide a correlation between the particular mutation (Arg-61) and AD.

Accordingly, in view of the quantity of experimentation necessary to make and use of mice comprising a modified apoE allele, wherein the modified allele encodes a modified apoE polypeptide that exhibits domain interaction characteristic of human apoE4 and the modified polypeptide comprises a Thr→Arg substitution at a position equivalent to amino acid 61 of the human apoE4, the lack of teaching or guidance provided by the specification with regard to the human apoE4 sequence,

the lack of teachings, guidance or a nexus between the observed phenotype of the claimed mice and AD, it would have required undue experimentation for one of skill in the art to make and/or use the claimed non-human animals and methods of using the same.

Claim Rejections - 35 USC § 112

The prior rejection of claims 1, 3, 5, 7, 14, 15, 20-22 under 112, 2nd paragraph, is withdrawn in view of Applicants' arguments.

Claim Rejections - 35 USC § 102

The prior rejection of claims 1, 3 and 5 under 35 U.S.C. 102(a) as being anticipated by Raffai *et al.* is withdrawn in view of the Weisgraber Declaration, which states that Bryan Tow is not an inventor of the instantly claimed invention. See p. 2, #4 of the Weisgraber Declaration, Exhibit 3.

Claim Rejections - 35 USC § 103

The prior rejection of claims 14, 15, 20-22 under 35 U.S.C. 103(a) as being unpatentable over Raffai *et al.* when taken with Mucke *et al.* is withdrawn in view of the Weisgraber Declaration, which states that Bryan Tow is not an inventor of the instantly claimed invention. See p. 2, #4 of the Weisgraber Declaration, Exhibit 3.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

tnt
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